UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,633	11/14/2006	Shite Sebastian	3265.1010-004	4672

45473 7590 10/07/2008

BRINKS, HOFER, GILSON & LIONE
2801 SLATER ROAD, SUITE 120
MORRISVILLE, NC 27560

EXAMINER	
OGUNBIYI, OLUWATOSIN A	
ART UNIT	PAPER NUMBER
1645	
MAIL DATE	DELIVERY MODE
10/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,633	SEBASTIAN ET AL.	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *13-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/14/06 and 9/10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-22 are pending in the application. Claims 1-12 are under examination

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Drawings

The drawings in this application have been accepted. No further action by Applicant is required.

Specification

The disclosure is objected to because of the following: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821-1.825 for the reason(s) because the amino acid sequence disclosed on p. 21 line 19 and p. 24 line 19 lacks the requisite sequence identifier (SEQ ID NO). Full compliance with the sequence rules is required in response to this office action.

Information Disclosure Statement

The information disclosure statements filed 11/14/06 and 9/10/07 have been considered. An initialed copy is enclosed.

Election/Restrictions

Applicant's election with traverse of Group I claims 1-12 and the species *S. aureus*, fluorescent materials, SEQ ID NO: 1 and wound dressing in the reply filed 8/7/08 acknowledged. The traversal is on the ground(s) that 37 C.F.R. § 1.475(b)(2) provides that an application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn, *inter alia,* a product and process of use of the product. Applicants urge that the present application includes claims directed to the use of detectably labeled synthetic serpin reactive site loop domain peptides as a substrate for detecting the presence or absence of a bacterium. The application also contains claims directed to biosensors including such detectably labeled synthetic serpin reactive site loop domain peptides and isolated peptides comprising detectable labels. The specification discloses that such products find use in the claimed methods. Thus, the claims are directed to products and processes for using such products and therefore have unity of invention.

Applicants argument is carefully considered but not found persuasive because the groups of inventions lack unity of invention because even though the inventions of these groups require the technical feature of a serpin reactive site loop domain peptide this technical feature is not a special technical feature as it does not make a contribution over the prior art in view of Travis et al (WO 00/63394, October 26, 2000). Travis et al teach a serpin reactive site loop domain peptide (see SEQ ID NO: 4, p. 6/6 of the drawings section of Travis et al) which is 100 % identical to a serpin reactive site loop domain peptide (see SEQ ID NO: 4 in fig. 1 and claim 22 of the instant application). Furthermore, detectable labels attached to said serpin reactive site loop domain peptide is prima facie obvious in the case of expressing said domain peptide with

tags known in the art (Jarvik et al Annu. Rev Genet. 1998. 32:601-18) at the time the instant invention was made (to facilitate isolation and identification of the protein. Thus, the technical feature linking the inventions of Groups I-III is not special within the meaning of PCT Rule 13.2 and therefore the Groups of invention lack unity.

The requirement is still deemed proper and is therefore made FINAL. Claims 13-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed 8/7/08.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for detecting the presence or absence of a bacterium, comprising the steps of: a) contacting a sample with a detectably labeled synthetic serpin reactive site loop domain peptide substrate under conditions that result in modification of said substrate by an enzyme produced by a bacterium; and

b) detecting a modification or an absence of the modification of the substrate, the modification of the substrate indicating the presence of the bacterium in the sample and absence of the modification of the substrate indicating absence of the bacterium in the sample.

There are many ways by which a peptide substrate can be enzymatically modified e.g. glycosylation, lipidation, proteolytic cleavage, phosphorylation, transamidation etc. For example, Kamalakkannan et al (Protein Engineering, Design and Selection vol. 17 no. 10, p. 721-729, 2004) teach bacterial enzymes that participate in lipid modification of proteins. The specification only provides written description for the instant method wherein the modification is the proteolytic cleavage by particular types of bacterial proteases that can cleave the RSL domain peptide of the serpin alpha-1-proteinase inhibitor (see p. 3 lines 1-4, p. 4 lines 28-33, p. 20 lines 10-14, p. 24 lines 29-33). The specification, however, does not have written description for a method or assay for detecting the presence or absence of a bacterium that utilizes detection of other types of modification (e.g. such as glycosylation, lipidation, phosphorylation, transamidation) of a detectably labeled synthetic serpin reactive site loop domain peptide substrate by a bacterial enzyme. Thus, Applicants as of the time of filing were not in possession of the instant method of detecting the presence or absence of bacteria which uses detection of

other types of modifications (apart from the disclosed proteolytic cleavage by particular bacteria proteases) of the RSL domain peptide of the serpin alpha-1-proteinase inhibitor by an enzyme produced by bacteria

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for detecting the presence or absence of a bacterium, comprising the steps of: a) contacting a sample with a detectably labeled synthetic serpin reactive site loop domain peptide substrate under conditions that result in modification of said substrate by an enzyme produced by a bacterium; and

b) detecting a modification or an absence of the modification of the substrate, the modification of the substrate indicating the presence of the bacterium in the sample and absence of the modification of the substrate indicating absence of the bacterium in the sample.

The breadth of claims covers the detection of any bacterium in any sample via the modification of any serpin reactive site loop domain (RSL) peptide by any enzyme produced by said bacterium.

The specification teaches that the RSL domain peptide of the serpin alpha-1-proteinase inhibitor is cleaved by culture or supernatants of cultures of the bacteria tested (See figures 2-8). The specification does not provide guidance as to RSL domains of other serpins that can be

cleaved by enzymes produced by bacteria. The specification teaches the sequence of the RSL domain of serpin alpha-1-proteinase inhibitor and its cleavage sites (see fig. 1A). However, not all proteins of the serpin family have this sequence unique to alpha-1-proteinase inhibitor. For example, Ngamkitidechakul et al (JBC 278:31796-31806, 2003, p. 31798) and Schick et al (PNAS 95: 13465-13470, 1998, p. 13466) teach RSL domains of other serpins which have sequences different from the RSL domain of the alpha-1-proteinase inhibitor. Nelson et al (cited in IDS: Analytical Biochemistry 260: 230-235 1998, p 235 column 2 second to the last sentence) teach that all of the serpins differ in amino acid constituents of the RSL. The specification does not teach whether bacteria produce enzymes that can cleave or modify other RSL domains of other serpins, thus it is unpredictable that the instant method can be practiced with any RSL loop domain from any other serpin. In addition, only bacterial enzymes with specificity for the cleavage sites of the RSL loop domain of alpha-1-proteinase inhibitor will be able to cleave or modify said RSL domain as evidenced by the cleavage sites depicted in Fig. 1A. Since all serpins differ in the RSL domain and there are many bacteria it would require a large amount of experimentation to screen all bacteria for enzymes specific for all the different RSL domains.

The specification contemplates the detection of the presence or absence of bacteria in a wound surfaces and body fluids (see p. 11 last bridging paragraph to p.12 lines 1-10). However, the instantly claimed method does not take into account that wound surfaces and body fluids comprise proteases (Steffensen et al Crit Rev Oral Biol Med 12(5):373-398, 2001, Armstrong et al J Am Podiatr Med Assoc 92(1): 12-18, 1998 and Ungar et al J Exp Med. 1961 January 31; 113(2): 359–380) that may be confounding factors in the instant method of bacterium detection. The specification in fig. 1A teaches that metalloproteinases (MMP1, MMP8 etc) from bacteria

such as *S. aureus* cleave the RSL peptide of alpha-1-proteinase inhibitor. However, host matrix metalloproteinases such as MMP8 play a role in wound healing and can be found in wound tissue. Even bacterial infection of a wound results in prolonged elevation of proinflammatory cytokines which in turn causes increases in levels of matrix metalloproteinases released from neutrophils and macrophages Cullen et al WO 03/040406 A2, 2003, p. 1 lines 24-28, p. 3 lines 8-15). The instant method as claimed does not control for cleavage of the RSL domain peptide by non-bacterial enzymes or proteases that may be present in wound surfaces and body fluids because the same type of bacterial enzymes that cleave RSL domain of alpha-1-proteinase inhibitor is present in wound surface. For example, since host matrix metalloproteinases e.g. MMP8, MMP1 are present in wound tissue and detection of cleavage of RSL by these host enzymes will not correctly indicate that bacteria is present in said wounds. Desrochers et al (J. Clin. Invest. 1991 88:2258-2265, see whole document especially fig.5) teaches that human MMP1 cleaves the RSL domain of alpha-1-proteinase inhibitor. The instantly claimed method does not distinguish between modification of RSL domain peptides by proteases produced bacteria and by host proteases present in wound surfaces and body fluids. Example 2 p. 18-19, in the specification teaches that wound dressings obtained from patients (no information on the wounds or patients was obtained) were extracted in PBS overnight and cleavage reaction was carried out on these samples with an RSL domain peptide of alpha-1-proteinase inhibitor. Figures 10A-D present the results from this assay and the figure legend states that the graphs illustrate the relative fluorescence of bacteria extracted from wound dressings. Since wound surfaces contain host enzymes that can cleave the detectably labeled RSL domain peptide it is not certain that the fluorescence observed is due to enzymes produced by bacteria. No

information on the wounds or patients was obtained and the samples were not cultured to determine that they were infected with bacteria. Furthermore it is not clear how figure 10A-D depicts relative fluorescence of bacteria since the detection signal is on the RSL domain peptide substrate and not on bacteria (p. 12 lines 11-32).

In view of the above considerations undue experimentation would be required of the skilled artisan to practice the invention as claimed.

Status of the Claims

Claims 1-12 are rejected. No claims allowed.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can normally be reached on M-F 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, either of the examiner's supervisors Shanon Foley (571-272-0898) or Robert Mondesi (571-272-0956) can be contacted.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Oluwatosin Ogunbiyi/

Examiner, Art Unit 1645

/Patricia A. Duffy/

Primary Examiner, Art Unit 1645